

4-SUBSTITUTED-2-HYDROXYBUTANOATES
AND A PROCESS FOR PRODUCING THEM

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The present invention relates to optically active 4-substituted-2-hydroxybutanoates which are useful chemical compounds as starting materials of medical supplies and to a process for producing them.

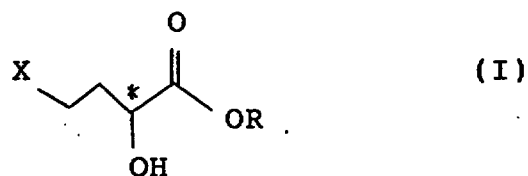
Optically active 4-substituted-2-hydroxybutanoates of the present invention are useful for starting materials of many medical supplies. However, there was no effective process so that racemic methyl 4-chloro-2-hydroxybutanoate, racemic methyl 4-bromo-2-hydroxybutanoate and the like were used (European Patent Laid-open Application No. 233728, etc.).

Lately, when racemic compounds are used as medical supplies, it is necessary to examine each physiological activity of two enantiomorphs, because the physiological activities may be different. Further, when a compound having a stereostructure especially has a strong physiological activity, it is earnestly required to construct only a compound having the desired stereostructure, considering the efficiency and safety.

The inventors of the present invention have developed optically active 4-substituted-2-hydroxybutanoates which become useful compounds as starting materials of pharmaceuticals, and they found an effective process for producing the esters.

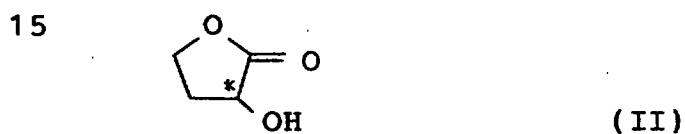
Namely, the present invention provides an optically active 4-substituted-2-hydroxybutanoate represented by the general formula:

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wherein X is Cl, Br, I or CN, R is alkyl of 1-10 carbon atoms, and * shows an asymmetric carbon.

Further, the present invention provides a process for producing said optically active 4-substituted-2-hydroxybutanoate represented by the general formula (I), which comprises ring-opening an optically active α -hydroxy- γ -butyrolactone as an intermediate compound of the formula:



wherein * shows an asymmetric carbon, and esterifying the compound obtained.

The following description illustrates this invention more specifically.

Optically active 4-substituted-2-hydroxybutanoates of the present invention are represented by the above general formula (I). As these compounds, the following compounds are exemplified:

R-methyl 4-chloro-2-hydroxybutanoate,
 R-ethyl 4-chloro-2-hydroxybutanoate,
 R-propyl 4-chloro-2-hydroxybutanoate,
 30 R-butyl 4-chloro-2-hydroxybutanoate,
 R-pentyl 4-chloro-2-hydroxybutanoate,
 S-methyl 4-chloro-2-hydroxybutanoate,
 S-ethyl 4-chloro-2-hydroxybutanoate,
 S-propyl 4-chloro-2-hydroxybutanoate,
 35 S-butyl 4-chloro-2-hydroxybutanoate,



- S-pentyl 4-chloro-2-hydroxybutanoate,
 R-methyl 4-bromo-2-hydroxybutanoate,
 R-ethyl 4-bromo-2-hydroxybutanoate,
 R-propyl 4-bromo-2-hydroxybutanoate,
 5 R-butyl 4-bromo-2-hydroxybutanoate,
 R-pentyl 4-bromo-2-hydroxybutanoate,
 S-methyl 4-bromo-2-hydroxybutanoate,
 S-ethyl 4-bromo-2-hydroxybutanoate,
 S-propyl 4-bromo-2-hydroxybutanoate,
 10 S-butyl 4-bromo-2-hydroxybutanoate,
 S-pentyl 4-bromo-2-hydroxybutanoate,
 R-methyl 4-iodo-2-hydroxybutanoate,
 R-ethyl 4-iodo-2-hydroxybutanoate,
 R-propyl 4-iodo-2-hydroxybutanoate,
 15 R-butyl 4-iodo-2-hydroxybutanoate,
 R-pentyl 4-iodo-2-hydroxybutanoate,
 S-methyl 4-iodo-2-hydroxybutanoate,
 S-ethyl 4-iodo-2-hydroxybutanoate,
 S-propyl 4-iodo-2-hydroxybutanoate,
 20 S-butyl 4-iodo-2-hydroxybutanoate,
 S-pentyl 4-iodo-2-hydroxybutanoate,
 R-methyl 4-cyano-2-hydroxybutanoate,
 R-ethyl 4-cyano-2-hydroxybutanoate,
 R-propyl 4-cyano-2-hydroxybutanoate,
 25 R-butyl 4-cyano-2-hydroxybutanoate,
 R-pentyl 4-cyano-2-hydroxybutanoate,
 S-methyl 4-cyano-2-hydroxybutanoate,
 S-ethyl 4-cyano-2-hydroxybutanoate,
 S-propyl 4-cyano-2-hydroxybutanoate,
 30 S-butyl 4-cyano-2-hydroxybutanoate,
 S-pentyl 4-cyano-2-hydroxybutanoate and the like.

The optically active 4-substituted-2-hydroxybutano-
 35 ates of the present invention are obtained by ring-open-
 ing optically active α -hydroxy- γ -butyrolactone represent-
 ed by the above formula (II) which is obtained by opti-

cally resolution wherein racemic α -hydroxy- γ -butyrolactone is transesterified with ethyl acetate, a fatty acid vinyl ester, a triglyceride or the like in the presence of an esterase produced by a microorganism or an esterase from an animal as a catalyst, and esterifying the compound obtained.

The racemic α -hydroxy- γ -butyrolactone of a raw material can be easily obtained from α -bromo- γ -butyrolactone by a method of Goal et al. (Organic Preparations and Procedures Int., 17, 91 (1985)).

As fatty acid vinyl esters used in the transesterification reaction, vinyl acetate, vinyl propionate, vinyl butyrate, vinyl caproate, vinyl laurate, etc. can be used. As triglycerides, triacetin, tripropionin, tributyrin, tricaproin, trilaurin etc. can be exemplified. These compounds are commercially available without any difficulty.

The following table shows commercially available esterases.

Table

<u>Trade name</u>	<u>Origin</u>	<u>Seller or Maker</u>
Lipase PS	<u>Pseudomonas fluorescens</u>	Amono Pharmaceutical Co., Ltd
Li-pase CES	<u>Pseudomonas sp</u>	"
Lipase AP	<u>Aspergillus niger</u>	"
Lipase M	<u>Mucor javanicus</u>	"
Lipase CE	<u>Humicola lanuginosa</u>	"
Lipase F-AP	<u>Rhizopus javanicus</u>	"
Lipase II	<u>Porcine Pancreas</u>	Sigma Chemical Co., Ltd
Lipase VIII	<u>Geotrichum Candidum</u>	"
Lipase X	<u>Rhizopus delamar</u>	"
Lipase	<u>Chromobacterium Viscosum</u>	Toyo Jozo Co., Ltd

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Lipase A	<u>Aspergillus niger</u>	Novo Industri A/S
Lipase	<u>Rhizopus niveus</u>	Nagase Biochemicals, Ltd.
Lipase B	<u>Pseudomonas fragi</u>	Sapporo Beer Co.

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In addition to these esterases, the enzymes produced from microorganisms can be used. These microorganisms which produce the enzymes having the above reaction ability can be used regardless of their species and 10 genus. As such microorganisms, the genera Pseudomonas, Arthrobacter, Acromobacter, Alcaligenes, Aspergillus, Chromobacterium, Candida, Mucor, Rhizopus, etc. can be exemplified.

In these microorganisms, particularly the genus 15 Pseudomonas is preferred.

The transesterification reaction is conducted by mixing a racemic α -hydroxy- γ -butyrolactone with ethyl acetate, a fatty acid vinyl ester or a triglyceride and by efficiently contacting the mixture with an esterase. 20 The reaction temperature is suitably from room temperature (about 10°C) to 150°C, especially and preferably from 20 to 45°C. The reaction time is from 1 to 1000 hours. α -hydroxy- γ -butyrolactone and ethyl acetate, the fatty acid vinyl ester or the triglyceride are suitably 25 mixed in the ratio from 1:0.5 to 1:10 by mole, preferably 1:0.5 by mole.

When necessary, n-hexane, n-heptane, benzene, toluene, ethyl ether, etc. can be used as a solvent by which esterase activity is not inhibited. The solvent may be 30 unused.

After the transesterification reaction is conducted, the esterase can be removed by conventional filter operation and used again, as it is. After concentrating the filtrate, optically active α -hydroxy- γ -butyrolactone and 35 an optically active α -acyloxy- γ -butyrolactone can be

separated by vacuum distillation or column chromatography, respectively. When these lactones have insufficient optical purities, each lactone is re-transesterified (in the case of the acyl compound, after the acyl group is hydrolyzed) to obtain a high optically pure compound.

The optically active α -hydroxy- γ -butyrolactone obtained can lead to the production of optically active 4-chloro-3-hydroxybutanoate or optically active 4-bromo-3-hydroxybutanoate by reaction with ethyl alcohol saturated with hydrogen chloride or hydrogen bromide.

Further, optically active α -hydroxy- γ -butyrolactone can lead to the production of optically active 4-iodo-2-hydroxybutanoate by reaction with trimethylsilyl chloride and sodium iodide or trimethylsilyl iodide.

Moreover, optically active α -hydroxy- γ -butyrolactone can lead to the production of optically active 4-cyano-2-hydroxybutanoate by reaction with trimethylsilylcyanide. Otherwise, it can lead to the production of optically active 4-cyano-2-hydroxybutanoate by cyanizing optically active 4-halo-2-hydroxybutanoate.

By using the above operation, R- and S-compound of optically active 4-substituted-2-hydroxybutanoate can be obtained, respectively.

Optically active 4-substituted-2-hydroxybutanoates of the present invention are useful and applicable compounds for starting materials of medical supplies. For example, optically active guanine derivatives (United States Patent Application US 4495190 etc.) which are useful for physiologically active materials can be obtained. Otherwise, as to calcium channel blockers (Japanese Patent Laid-open Application No. 61-87503, etc.), optically active materials by which more effective activity is expected can be obtained.

The following examples illustrate the present inven-



tion more specifically, but these will not always be precise in practical applications.

Example 1

(i) Production of R-(+)- α -hydroxy- γ -butyrolactone

5 A mixture of 15.3 g of racemic- α -hydroxy- γ -butyrolactone, 6.5 g of vinyl acetate and 5 g of lipase PS (manufactured by Amano Pharmaceutical Co., Ltd.) was put into a 100 ml flask. The mixture was stirred for 6 hours at room temperature. After lipase PS was removed by
10 filtration, the filtrate was concentrated and about 40 g of liquid was obtained. The liquid was column-chromatographed (toluene/ethyl acetate (10/1)), and 5.2 g of S-(-)- α -hydroxy- γ -butyrolactone ($[\alpha]_D$ -57.6° (c 1.22, CHCl₃), 99%ee) and 7.2 g of R-(+)- α -acetyloxy- γ -butyro-
15 lactone ($[\alpha]_D$ +32.6° (c 0.87, CHCl₃), 70%ee) were separated, respectively.

R-(+)- α -acetyloxy- γ -butyrolactone was dissolved into a mixed solvent of 50 ml of 1,4-dioxane and 30 ml of ethanol, and 3.8 g of potassium carbonate was added. The
20 mixture was stirred for 5 hours at room temperature. After the mixture was neutralized with hydrochloric acid, the salt separated was removed by filtration. Moreover, after removing ethanol, the filtrate was purified by distillation, and 6.1 g of R-(+)- α -hydroxy- γ -butyrolac-
25 tone was obtained.

(ii) Production of R-ethyl (+)-4-chloro-2-hydroxybutanoate

1.6 g of R-(+)- α -hydroxy- γ -butyrolactone (90%ee) was dissolved into 200 ml of ethanol, and the solution was
30 put into a 300 ml three-necked flask. Hydrogen chloride gas was blown into the three-necked flask, and the solution was stirred in a saturated condition at room temperature overnight. After hydrogen chloride gas was removed thoroughly by blowing nitrogen through the solution,
35 ethanol was distilled away, and the residue was extracted

with ether. The ether layer was washed with sodium bicarbonate and then with a saturated saline solution. After the ether layer was dried on anhydrous magnesium sulfate, ether was distilled away. The residue was distilled under
 5 reduced pressure to obtain 2.1 g of the desired R-ethyl (+)-4-chloro-2-hydroxybutanoate. The physical properties of the compound are as follows.

Boiling point: 112°C/17 mmHg

Specific rotation: $[\alpha]_D +6.1^\circ$ (C1.9, CHCl_3)

10 Example 2

Production of S-ethyl (-)-4-chloro-hydroxybutanoate

1.6 g of S-(-)- α -hydroxy- γ -butyrolactone (90%ee) was dissolved into 200 ml of ethanol, and the solution was put into a 300 ml three-necked flask. Hydrogen chloride
 15 gas was blown into the three-necked flask, and the solution was stirred in a saturated condition at room temperature overnight. After hydrogen chloride gas was removed thoroughly by blowing nitrogen through the solution, ethanol was distilled away, and the residue was extracted
 20 with ether. The ether layer was washed with sodium bicarbonate and then with a saturated saline solution. After the ether layer was dried on anhydrous magnesium sulfate, ether was distilled away. The residue was distilled under reduced pressure to obtain 2.0 g of the desired S-ethyl
 25 (-)-4-chloro-2-hydroxy butanoate. The physical properties of the compound are as follows.

Boiling point: 101°C/13 mmHg

Specific rotation: $[\alpha]_D -6.7^\circ$ (C1.2, CHCl_3)

Example 3

30 Production of R-ethyl (+)-4-iodo-2-hydroxybutanoate

20 ml of an acetonitrile solution of trimethylsilyl chloride was slowly added into 50 ml of an acetonitrile solution containing 1.3 g of R-(+)- α -hydroxy- γ -butyrolactone (70%ee) and 5.7 g of sodium iodide. After the
 35 solution was heated under reflux for 14 hours, 10 ml of

ethanol was added dropwise and the solution was stirred at room temperature for 10 minutes.

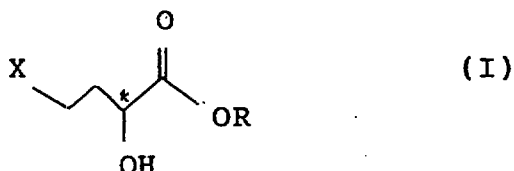
Acetonitrile was distilled away, and ether was added to the residue. The ether layer was washed with sodium
5 bicarbonate and then with a saturated saline solution. After the ether layer was dried on anhydrous magnesium sulfate, ether was distilled away. 0.73 g of the desired R-ethyl (+)-4-iodo-2-hydroxybutanoate was obtained. Specific rotation: $[\alpha]_D +4.0^\circ$ (C1.15, CHCl_3)

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Claims:

1 An optically active 4-substituted-2-hydroxybutanoate represented by the general formula:

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10 wherein X is Cl, Br, I or CN, R is alkyl of 1-10 carbon atoms, and * shows an asymmetric carbon.

2 The compound as claimed in Claim 1, wherein X is Cl.

3 The compound as claimed in Claim 1, wherein X is
15 I.

4 A process for producing an optically active 4-substituted-2-hydroxybutanoate represented by the general formula (I) as claimed in claim 1, characterized in that it comprises ring-opening a compound of the formula:

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25 wherein * shows an asymmetric carbon, and esterifying the compound obtained.

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